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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	12

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/214,913	Applicant(s) SMITH ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/16/1999; 6/13/2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32, 34-37, 39, 41-45, 47-48 and 50-52* is/are pending in the application.

4a) Of the above claim(s) *12, 18, 25, 29-32, 34, 39, 42- 43, 45, 48, 51 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-17,19-24,26-28,35-37,41,44,47 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ [illegible]
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ [illegible]

DETAILED ACTION

1. Claims 1-32, 34-37, 39, 41-45, 47-48 and 50-52 are pending.

2. Applicant elected Group VI, claims 1-24, 26-28, 35-37, 41, 44, 47 and 50 drawn to basic amino acid sequence GSSKSPSKKKKKKPGD. It is noted that Claim 12 recited membrane binding element is a ligand of a known integral membrane protein and claim 18 recited a soluble derivative of SEQ ID NO: 2 were inadvertently placed in the same group. Upon reconsideration, the prior art search has been extended to cover Group I that reads on the membrane binding element is a fatty acid derivative from aliphatic acyl group about 1-18 methylene unit, Group V that reads on the basic amino acid membrane binding element is DGPKKKKKKSPSKSSG, Group VII that reads on the membrane binding element is SPSNETPKKKKKKRFSFKKSG, Group VIII that reads on the membrane binding element is DGPKKKKKKSPSKSSK, Group IX that reads on the membrane binding element is SKDGKKKKKKSKTK, and DGPKKKKKKSPSKSSGC, GSSKSPSKKKKKKPGDC, CDGPKKKKKKSPSKSSK, and SKDGKKKKKKSKTKC as recited in claim 21 and Group XIII that reads on the soluble polypeptide is prourokinase, Group XIV that reads on the soluble polypeptide is streptokinase, Group XV that reads on the soluble polypeptide is tissue-type plasminogen activator, and Group XVIII that reads on the soluble polypeptide is complement inhibitors selected from complement regulatory proteins and hybrids or muteins thereof. Accordingly, Claims 1-9, 10, 11, 13-17, 19-24, 26-28, 35-37, 41, 44, 47 and 50 drawn to a soluble derivative comprising two or more heterologous membrane binding elements associated with a polypeptide wherein the membrane binding element is fatty acid derivative from aliphatic acyl group about 1-18 methylene unit, wherein the basic amino acid membrane binding element is GSSKSPSKKKKKKPGD, DGPKKKKKKSPSKSSG, SPSNETPKKKKKKRFSFKKSG, DGPKKKKKKSPSKSSK, SKDGKKKKKKSKTK, DGPKKKKKKSPSKSSGC, GSSKSPSKKKKKKPGDC, CDGPKKKKKKSPSKSSK, or SKDGKKKKKKSKTKC and wherein the soluble polypeptide is prourokinase, streptokinase, plasminogen activator, complement regulatory proteins and hybrids or muteins thereof and a pharmaceutical composition for hyperacute allograft rejection associated

3. Applicant's election with traverse of Group VI, claims 1-24, 26-28, 35-37, 41, 44, 47 and 50, filed 6/18/01, is acknowledged. The traversal is on the ground(s) that Groups XXVII, XXIX, XXX and XXXI should be examined together because the Hebell reference does not teach a soluble derivative of a soluble polypeptide wherein the polypeptide is bound to heterologous binding elements with low membrane affinity such as those employing myristoyl and hence the restriction should not be based on the lack of unity of invention. However, Sigal *et al* teach a membrane targeting motif consists of myristoyl group (Myr) and a hydrophilic amino acid sequence rich with positively charged lysine residues (Myr-GSSKSKPKDPSQRRR) (See page 12253, column 1, in particular). Sigal *et al* further teach that a peptide containing myristoyl group alone binds to phospholipid vesicles (artificial membrane) with an apparent dissociation constant Kd of 10^{-4} M (low membrane affinity) whereas a peptide containing five basic residues binds to phosphatidycholine/phosphatidyserine (artificial membrane) with a Kd of 10^{-3} M (low membrane affinity) as applied to instant claims 1, 6-9 (See Fig 1, pages 476, page 477 column 2 first paragraph, in particular). Therefore, the requirement is still deemed proper and is therefore made FINAL.

4. Claims 12, 18, 25, 29-32, 34, 39, 42-43, 45, 48 and 51-52 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

5. Applicant should amend the first line of the specification to reflect the relationship between the instant application and PCT EP 97/03715, filed 7/8/1997.

6 This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

7. The disclosure is objected to because of the following informalities: (1) arrangement of the specification; (2) the formula for "% inhibition" on pages 50 and 53 is incorrect. The correct formula is "$1-[(A-A_0)/Amax-A_0)) \times 100$".

8. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

9. Claims 10 and 36 are objected to because of the following informalities: (1) typographical errors "aminoacid" as recited in claim 10 and "nd" as recited in claim 36. Appropriate correction is required.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-11, 13-17, 19-20, 23, 26-28, 35-37, 41, 44 and 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the

derivative" of any "soluble polypeptide" wherein said "soluble derivative" comprising two

more "heterologous membrane binding elements" wherein the binding elements are not all identical as recited in claim 1 and selected from the group consisting of (2) *any* "fatty acid derivative" which is also a "non-peptidic membrane-binding entity" as recited in claims 8-9 and 14 (3) *any* "basic amino acid sequence" or "peptidic membrane binding element" as recited in claims 1-8, 10, 14-15, 26 and 35 (4) *any* "polypeptide" as recited in claims 1, 27 (5) *any* "complement inhibitors from complement regulatory proteins" and "hybrids" or "muteins thereof" as recited in claims 13 and 19; (6) *any* "fragment" of soluble CR1 polypeptide as recited in claim 19-20 and 44, (7) *any* "thrombolytic agent" as recited in claim 23 and 47, *any* "derivative" as recited in claims 26-28, 37, since the base claim 1 requires at least two or more membrane binding elements covalently associated with a polypeptide and *any* "compound" as recited in claim 36. There is also a lack of written description about (8) *any* "chemical bridging groups "-A-R-B-" associated with *any* soluble derivative as recited in claims 16-17 since the base claim 1 requires the polypeptide be "covalently linked" with two or more membrane binding elements.

The specification discloses only a soluble derivative of a soluble polypeptide consisting of only two heterologous membrane binding elements wherein one the membrane binding elements is a myristoyl fatty acid with 12 methylene units and a basic polylysine amino acid sequence selected from the group consisting of GSSKSPSKKKKKKPGD, DGPKKKKKKSPSKSSG, SPSNETPKKKKKKRFSFKKSG, DGPKKKKKKSPSKSSK, SKDGKKKKKKSKTK, DGPKKKKKKSPSKSSGC, GSSKSPSKKKKKKPGDC, CDGPKKKKKKSPSKSSK, or SKDGKKKKKKSKTKC which is covalently associated with a soluble complement receptor (SCR1-3) (SEQ ID NOS: 7-14 and 17), or a conjugate of Streptokinase (SEQ ID NO: 21), or a plasminogen activator (SEQ ID NO: 22) for **in vitro assays** such as inhibition of complement-mediated lysis (pages 50-52), plasminogen activator assay (page 53) and erythrocyte binding assays (See pages 54-57).

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claims 1-11, 13-17, 19-20, 23, 26-28, 35-37, 41, 44 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "heterologous" as recited in claim 1 in conjunction with the phrase "not all identical" renders the claim ambiguous because "heterologous" means they are different and yet "not all identical" indicating at least some are the same.

The phrases "thermodynamic additivity" as recited in claim 1 renders the claim ambiguous and indefinite because it is unclear what are the metes and bounds of the term "**thermodynamic additivity**" since the specification does not defines the term.

The term "**for specific membranes**" as recited in claim 4 renders the claim ambiguous and indefinite because it is not clear which membrane applicant refers to, i.e., cell membrane, nuclear membrane, membrane of the organelle or artificial membrane.

The phrase "(N-terminus on left)" as recited in claims 10 and 48 is redundant because it is a convention that the N-terminus of a polypeptide be on the left.

The recitation of "a flexible linker group" in claim 14 and "linker group" in claim 15 is indefinite and ambiguous because base claim 1 requires the binding elements to be "covalently" associated.

The "bridging group" recited in claim 16 has no antecedent basis in claim 14.

It is suggested that claim 28 be rewritten as "a polypeptide portion of a derivative according to claim 1, wherein the polypeptide is selected from the group consisting of SEQ ID NO: 7, 23, 33, 6 and 14".

The phrase "(optionally C-substituted)" as recited in claim 35 renders the claim indefinite and ambiguous because it is not clear "optionally C-substituted" in the parenthesis is part of the claimed invention. Furthermore, it is not clear what applicant meant by "optionally C-substituted". Is it substitution at the carboxy-terminus? If it is, what is being substitute and substitute for what?

The [illegible] recited in claim 36 is indefinite because only a soluble derivative of a

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

15. Claims 1-3, 5-10, 14-15 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Sigal *et al*, (Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892).

Sigal *et al* teach a membrane targeting motif consists of myristoyl group (Myr) and a hydrophilic amino acid sequence rich with positively charged lysine residues (Myr-GSSKSKPKDPSQRRR) (See page 12253, column 1, in particular). Sigal *et al* further teach that a peptide containing myristoyl group alone binds to phospholipid vesicles (artificial membrane) with an apparent dissociation constant Kd of 10^{-4} M (low membrane affinity) whereas a peptide containing five basic residues binds to phosphatidycholine/phosphatidyserine (artificial membrane) with a Kd of 10^{-3} M (low membrane affinity). However, a peptide containing both the myristoyl group (Myr) and the amino acid sequence rich in positively charged amino acid residues such as lysine residues that bind to membrane with a Kd of 10^{-7} M, indicating that the hydrophilic and electrostatic binding energy are additive (see page 12253, column 2, in particular). Claims 14-15 are included in this rejection because the linker group as defined in the specification could be any unspecified amino acids that forms a peptide bond which reads on the prior art.

Because the reference membrane binding elements have the same structure as the claimed membrane binding elements, the binding properties of the reference membrane binding elements (myristate and lysine) are inherent. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980). Claim 3 is included in this rejection because each membrane binding element is small, with a maximum number of 20 amino acids for the peptidic binding element wherein each amino acid residue is roughly equal to about 100 Dalton, which is about 2 kDa (20 x 100 = 2,000

[illegible] rejection because lipid and high ionic strength (salt) solution are known for their use as a

pharmaceutical carrier because of their solubility. The peptidic membrane binding element (basic amino acid sequence) is located at the N terminus of the soluble polypeptide linking together via a peptide bond. The transitional phrase "comprising" in claim 1 is open-ended. It opens up the claims to read on additional amino acid residues. Thus, the reference teachings anticipate the claimed invention.

16. Claims 1-3, 6-11, 14-15 and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 5,776,689 (filed July 1996, PTO 892).

The '689 patent teaches a fusion polypeptide consisting of two heterologous membrane binding elements (Myristyolation signal, M) and a basic amino acid sequence which is rich in lysine residues covalently associated with a polypeptide wherein the membrane elements are fatty acid derivative such as the Myristoyl group of the myristic fatty acid which has low membrane binding affinity and a basic amino acid sequence SKDGKKKKKKSKTKCVIM (See Figure 1, column 8 line 57, SEQ ID NO: 2 of '689, column 10, line 3-7, in particular). The said fatty acid is from aliphatic acyl group with about 12 methylene units and the basic amino acid sequence includes 6 lysine (K) residues, which is within the range of n equal to about 3 to 10. The peptidic membrane binding element (basic amino acid sequence) is located at the N or the C terminus of the soluble polypeptide linking together via a peptide bond (See Fig 1, in particular). The derivative has at least one element is hydrophilic (polylysine) and comprises at least two membrane binding elements which are the fatty acid and polylysine basic amino acid sequence. The transitional phrase "comprising" in claim 1 is open-ended. It opens up the claims to read on additional amino acid residues. The '689 patent further teaches that a fusion protein containing one of the membrane binding elements will localize the fusion protein to the plasma membrane (See column 8, lines 65-67 bridging column 9, lines 1-2, in particular). Because the reference membrane binding elements have the same structure as the claimed membrane binding elements, the binding properties of the reference membrane binding elements (myristate and lysine) are inherent. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980). Claim 2 is included in this rejection because of the inherent properties of each binding element is low

2,000 or 2 kDa) and the molecular weight of a myristic fatty acid which is about 228. The combine membrane elements have a molecular weight of less than 5kDa. Claims 14-15 are included in this rejection because the linker group as defined in the specification could be any unspecified amino acids that forms a peptide bond which reads on the prior art.
Thus, the reference teachings anticipate the claimed invention.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1, 13, 19-20, 37, 41 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigal *et al*. (Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892) in view of US Pat No. 5,472,939, (Dec 1995, PTO 892).

The teaching of Sigal *et al* has been discussed supra.

The claimed invention of claim 13 differs from the references only by the recitation of the soluble polypeptide is a complement inhibitor.

The claimed invention of claim 19 differs from the references only by the recitation of the soluble polypeptide is a soluble complement inhibitor.

The claimed invention of claim 20 differs from the references only by the recitation of

The claimed invention of claim 37 differs from the references only by the recitation of a pharmaceutical composition comprising a derivative of claim 1 in combination with a pharmaceutical acceptable carrier.

The claimed invention of claim 41 differs from the references only by the recitation of a pharmaceutical composition for treating a disease or disorder associated with inflammation or inappropriate complement activation comprising a therapeutically effective amount of a derivative of a soluble complement inhibitor and a pharmaceutically acceptable carrier or excipient.

The claimed invention of claim 44 differs from the references only by the recitation of a pharmaceutical composition for treating a disease or disorder associated with inflammation or inappropriate complement activation comprising a therapeutically effective amount of a soluble CR1 polypeptide derivative, which is a soluble CR1 polypeptide fragment and a pharmaceutically acceptable carrier or excipient.

The '939 patent teaches a soluble complement regulatory protein sCR1 which has a short consensus structure motif that binds to a complement component for reducing tissue damage associated with myocardial infarction (See column 8, lines 15-40, column 9, lines 29 and 43-44, column 67, 68, 69 and Abstract, in particular). The '939 patent further teaches a fusion protein comprising a portion of the CR1 sequence plus a non-CR1 sequence (See column 21, lines 39-42). The '939 patent teach other deletion mutants of CR1 which are functional derivatives (See column 16, lines 41-58, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently link the binding elements as taught by Sigal *et al* with the soluble complement inhibitor for a pharmaceutical composition consisting of a soluble derivative of a soluble complement comprising two or more heterologous membrane binding elements wherein the binding elements are a basic amino acid sequence and a myristoyl group covalently associated with the soluble complement receptor (CR1) or a functional derivative thereof.

One having ordinary skill in the art would have been motivated to use a soluble complement receptor inhibitor which is a soluble (CR1) peptide fragment or a functional derivative as taught by the '939 patent because the '939 patent teaches that a soluble CR1

that a peptide containing both the myristoyl group (Myr) and the positively charged lysine residues can enhance the binding of the soluble polypeptide to the membrane because the hydrophilic and electrostatic binding energy are additive (see page 12253, column 2, in particular).

20. Claims 1, 13, 23-24, 37, 47 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigal *et al*, (Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892) in view of EP 0,207,589 A1, (Jan 1987, PTO 892) or EP 0,155,387 A2 (Sept 1985, PTO 892) or US Pat No 5,326,700 (July 1994, PTO 892).

The teaching of Sigal *et al* has been discussed supra.

The claimed invention of claim 13 differs from the references only by the recitation of the soluble polypeptide is a prourokinase, streptokinase, or tissue-type plasminogen activator.

The claimed invention of claim 23 differs from the references only by the recitation of the soluble polypeptide is a thrombolytic agent.

The claimed invention of claim 24 differs from the references only by the recitation of the soluble polypeptide is a SEQ ID NO: 22, which is a tissue plasminogen activator.

The claimed invention of claim 37 differs from the references only by the recitation of a pharmaceutical composition comprising a derivative of claim 1 in combination with a pharmaceutical acceptable carrier.

The claimed invention of claim 50 differs from the references only by the recitation of a pharmaceutical composition for treating thrombotic disorders comprising a therapeutically effective amount of a soluble derivative of SEQ ID NO: 22.

The claimed invention of claim 47 differs from the references only by the recitation of a pharmaceutical composition for treating thrombotic disorders comprising a therapeutically effective amount of a derivative wherein the derivative is prourokinase, streptokinase or tissue-type plasminogen activator and a pharmaceutically acceptable carrier or excipient.

The EP 0207,589 A1 patent teaches tissue type plasminogen activator, functional derivatives thereof such as urokinase (see page 10, in particular) and pharmaceutical compositions for treatment of thrombotic diseases (See page 6, lines 39-42).

The '700 patent teaches a tissue plasminogen activator having an amino acid sequence identical to SEQ ID NO: 22 of the instant application (See column 39, SEQ ID NO: 16 of '700, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently link the membrane binding elements as taught by Sigal *et al* with the tissue type plasminogen activator, or functional derivatives thereof such as urokinase as taught by the EP 0207,589 A1 patent or the hybrids of plasmin linked to urokinase plasminogen activator B-chain as taught by the EP 0,155,387 A2 patent or the tissue plasminogen activator as taught by the '700 patent for a soluble derivative comprising the myristoylated basic amino acid sequence covalently linked to a tissue type plasminogen activator, tissue factor, urokinase plasminogen activator for treating thrombotic disease.

One having ordinary skill in the art would have been motivated to use the tissue type plasminogen activator, or functional derivatives thereof and hybrid as taught by the EP 0207,589 A1 patent or the EP 0,155,387 A2 patent or the plasminogen activator as taught by the '700 patent because the said soluble plasmin, derivative and hybrids thereof, or the plasminogen activator can be used for treating thrombotic disease. Sigal *et al* teach that a peptide containing both the myristoyl group (Myr) and the positively charged lysine residues can enhance the binding of the soluble polypeptide to the membrane because the hydrophilic and electrostatic binding energy are additive (see page 12253, column 2, in particular).

21. Claims 1 and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigal *et al*, (Proc. Natl. Acad. Sci. USA 91: 12253-12257, Dec 1994; PTO 892) in view of EP 0152736 A2 (Aug 1985; PTO 892).

The teaching of Sigal et al has been discussed supra.

The combined teachings differ from the claimed invention by not using the chemical bridging groups having the formula (I): -A-R-B- in which each of A and B, which may be the same or different, represents -CO-, -C(=NH2+)-, maleimido, -S-, or a bond and R is a bond or a linking group containing one or more -(CH2)- or meta-, ortho- or para- disubstituted phenyl units optionally together with a hydrophobic portion or the R is selected from -(CH2)r-, -(CH2)p-S-S-

The EP 0152736 patent teaches an enzyme-protein conjugate using bridging groups having a formula of (I): -A-R-B- in which each of A and B, which may be the same or different, represents -CO-, -C(=NH2+)-, maleimido, -S-, or a bond and R is a bond or a linking group containing one or more -(CH2)- or meta-, ortho- or para- disubstituted phenyl units optionally together with a hydrophobic portion; the R is selected from -(CH2)r-, -(CH2)p-S-S-(CH2)q- (See pages 2-3, 31, in particular). The EP 0152736 patent further teaches the enzyme-protein conjugates made using the method mentioned above are suitable as a pharmaceutical composition (See page 11, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the covalently link heterologous membrane binding elements with a soluble polypeptide as taught by Sigal *et al* with a chemical cross linking group as taught by the EP 0152736 patent for a soluble peptide derivative.

One having ordinary skill in the art would have been motivated to use the bridging group as taught by the EP 0152736 patent because the derivative or conjugates made using these bridging group are suitable for pharmaceutical compositions (See page 11, in particular).

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

24. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
Aug 27, 2001

CHRISTINA Y. CHAN
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